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REVIEW ARTICLES

Subacute Stent Thrombosis: Evolving Issues and Current Concepts

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During percutaneous coronary revascularization, intracoronary stents are effective in the treatment of abrupt vessel closure and improvement of suboptimal angioplasty results, and compared to balloon angioplasty, they reduce stenosis recurrence. Opposing these benefits, subacute thrombosis of stents is associated with a substantial increase in periprocedural morbidity and mortality. To review factors associated with stent thrombosis and to study the impact of evolving procedural techniques on the incidence of stent thrombosis, we reviewed all English articles from MEDLINE (1988 to 1995) with key words "stent" and "thrombosis." Stent registry data and recent abstracts from scientific meetings were also reviewed. Factors related to the clinical setting, the lesion, the stent and the procedural technique that affect the risk of stent thrombosis were identified. Sixty clinical studies were reviewed and include 7,914 patients receiving intracoronary stents. Studies were separated into those reporting stents placed emergently or electively without adjunct high-pressure balloon inflations, stents placed in saphenous vein graft conduits, and stents placed with high-pressure balloon inflations but without subsequent oral anticoagulants. Overall, subacute thrombosis was substantially higher in stents placed emergently (10.1%) compared to those placed electively (4.3%). Among contemporary trials employing high-pressure balloon inflations, the rate of stent thrombosis appears markedly lower (1.3%) despite reduced postprocedural anticoagulation. Taken together, these studies suggest factors associated with a heightened risk of stent thrombosis, many of which can be avoided with proper case selection and contemporary techniques.

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Although the success of percutaneous transluminal coronary revascularization has steadily improved over the past two decades, abrupt vessel closure in the hours postprocedure and restenosis in the months postprocedure remain the major limitations. Intracoronary stent placement has gained substantial recent popularity to address these limitations. In 1987, Sigwart and colleagues (1) were first to report successful implantation of intracoronary stents in patients. Early series demonstrated a high rate of procedural success, though this was opposed by an alarmingly high rate of stent thrombosis within the first month after revascularization (2). Stent thrombosis quickly became a major concern and prompted widespread study.

The mechanisms of stent thrombosis are not fully understood, but a number of associated factors are intuitive. Intravascular stents are metallic and thus thrombogenic. Similarly, vessel injury during percutaneous revascularization exposes underlying collagen and tissue factor, which activate platelets and the extrinsic coagulation cascade. These events, as well as ruptured plaque and thrombus known to be present in acute coronary syndromes, are believed to be key contributors to stent thrombosis. A principal factor thought to be responsible for the high stent thrombosis rate during the early stent experience was inadequacy of anticoagulation and antiplatelet therapy (2). In a randomized study of 42 dogs, Palmaz and colleagues (3) reported that platelet deposition was lowest on intravascular stents in the group treated with a combination of heparin, aspirin, dipyridamole, and dextran compared to dogs treated with heparin alone or heparin and aspirin. Likewise, an early clinical experience with the Palmaz–Schatz stent revealed that fewer than 1% of 174 patients who received oral anticoagulation developed subacute closure compared to 18% of 39 patients who received only antiplatelet therapy (4). Consequently, intense anticoagulation regimens were established, including heparin, dextran, aspirin, dipyridamole and warfarin. Not surprisingly, this engendered a substantial increase in bleeding complications. More recently, technical factors associated with stent deployment and proper vessel selection are believed to be of greater importance to stent thrombosis than adequacy of anticoagulation. Current stent deployment techniques appear to have markedly reduced the relative risk of thrombosis. This paper reviews factors associated with stent thrombosis and contemporary preventive strategies.

Incidence

Initial series of stent placement (2,4) reported a disappointingly high (~25%) occurrence of thrombotic stent closure.

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Table 1. Subacute Stent Thrombosis After Elective Stent Placement

First Author or Trial Name (ref no.)	Year	No. of Patients	Stent	Thrombosis (no. [%] of patients)
Cross-Sectional Studies				
Schatz (4)	1991	226	P/S	8 (3.7)
Carrozza (6)	1992	220	P/S	1 (0.5)
Fajadet (8)	1992	282	P/S	13 (4.6)
Nath (7)	1993	14	G/R	4 (28.6)
Kimura (9)	1993	74	P/S	1 (1.4)
Sutton (11)	1994	224	G/R	8 (3.6)
Savage (5)	1994	300	P/S	14 (4.7)
Eeckhout (13)	1994	92*	Mixed	5 (5.4)
Foley (25)	1994	99	P/S	1 (1.0)
Whitlow (26)	1994	244	Wiktor	24 (9.8)
Pooled	1991–1994	1,775	Mixed	79 (4.5)
Randomized Trials				
STRESS (26)	1994	205	P/S	7 (3.4)
BENESTENT (27)	1994	259	P/S	9 (3.5)
TASC I (28)	1994	133	P/S	6 (4.5)
Pooled	1994	597	P/S	22 (3.7)

*Number of stents. BENESTENT = Belgium and Netherlands Stent Study Group; G/R = Gianturco-Roubin; P/S = Palmaz-Schatz; ref = reference; STRESS = Stent REStenosis Study Group; TASC I = Trial of Angioplasty and Stents in Canada.

Subsequent studies have been progressively more encouraging, with a range of subacute stent thrombosis from 0.5% to 29% (pooled average 4.4%) (Table 1) (4–13), suggesting there was a period of learning for operators, improvement in stent deployment techniques and enhanced post-procedural care (4,7). Evidencing this, George et al. (14) estimated that the rate of stent thrombosis in their series of patients treated for threatened vessel closure was 12% from September 1988 to March 1990, 11% from March 1990 to September 1990 and 5% from September 1990 to June 1991. More recently, in the STRESS (STent REStenosis Study) study (15) in which 410 patients were randomized to receive either stents or conventional balloon angioplasty, the incidence of subacute stent thrombosis was even lower (3.4%). In fact, although the sample size is small, this low rate of subacute stent thrombosis was not statistically different from the abrupt vessel closure rate among patients undergoing balloon angioplasty (1.5%). Similarly designed prospective studies, the BENESTENT (BElgium and NEtherlands STENT) Study Group (n = 520) (16) and TASC I (Trial of Angioplasty and Stents in Canada, n = 266) (17), corroborated this observation with rates of subacute stent thrombosis of 3.5% and 4.5%, respectively. Subacute stent thrombosis rates continue to decrease, and current efforts are targeting a rate of ≤1%.

Timing

Acute stent thrombosis usually occurs within minutes to hours, whereas *subacute* stent thrombosis occurs within days to weeks after stent deployment (7). Stent thrombosis rarely occurs acutely, i.e., within the first 24 h following stent placement. When results of nine studies (4,6,7,18–23), including 1,383 patients, are pooled, only 8 (0.6%) episodes of acute stent thrombosis were reported, whereas there were 89 (6.4%) episodes of subacute thrombotic stent closure. Patients with acute stent thrombosis are usually still in the hospital and frankly symptomatic. Thus, they are quickly diagnosed and treated. On the other hand, subacute stent thrombosis, which represents the majority of thrombotic stent closure, can be somewhat insidious, occurring in patients 2 to 30 days following stent placement. Schömig and colleagues (24) observed that 43% of patients with subacute stent thrombosis present within the first week, and over 80% by the second week. The modal presentation was between days 5 and 6 following stent placement (7,15). Because many patients with subacute stent thrombosis have been discharged from the hospital, rapid restoration of coronary arterial flow is often not possible, and patients may sustain acute myocardial infarction or even death. Indeed, pooled data from numerous trials show rates of myocardial infarction and death following stent thrombosis of 61% and 12%, respectively. Therefore, the management of stent thrombosis requires rapid restoration of antegrade flow mechanically (emergency bypass surgery or angioplasty) or pharmacologically (thrombolytic therapy).

Factors Associated With Stent Thrombosis

Similar to the formative years of balloon angioplasty, much of the early understanding of stent thrombosis has been obtained from retrospective studies and registry data, although recent insight is emerging from prospective randomized trials. A number of factors associated with stent thrombosis are being defined and can be broadly categorized as related to the patient, the lesion, the stent and the technique of deployment (Fig. 1).

Patient-related factors. The risk for subacute stent thrombosis is related to several patient-specific factors such as clinical presentation (stable angina vs. acute coronary syndrome) and hemodynamic stability (coronary perfusion pressure and flow). In these different clinical subsets of patients, there may be varied potential of thrombogenicity and resultant subacute stent thrombosis.

Indication for stent deployment. Intracoronary stents may be deployed electively (4–13) (Table 1) or as a "bail-out" procedure during threatened or abrupt vessel closure (6–14,18–21,24–34) (Table 2). Stents may also be placed electively to reduce restenosis (15,16) or as an adjunct therapy to improve suboptimal angioplasty results (11,29,31,34,35). The pooled rate of subacute stent thrombosis following elective stent deployment in 598 patients in the STRESS (15), BENESTENT (16) and TASC I (17) studies was 3.7%. These results were obtained in hemodynamically stable patients with lesions that were discrete in large, nontortuous native vessels, without the presence of intraluminal thrombus or involvement of ostium or bifurcation.

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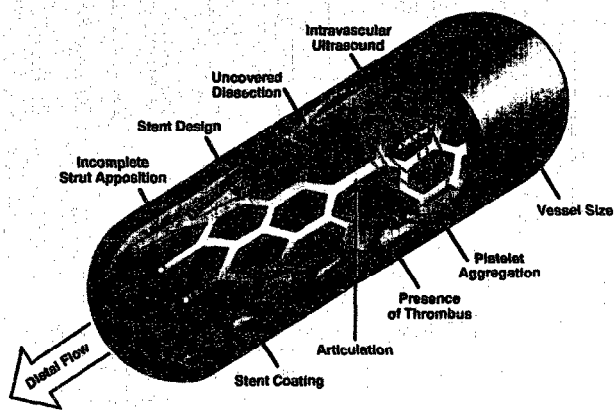

Figure 1. Schematic diagram showing factors related to subacute stent thrombosis.

The observed occurrence of subacute stent thrombosis has been substantially higher when stents were deployed emergently, i.e., during threatened or abrupt vessel closure. Under these circumstances, the intravascular milieu can be highly thrombogenic from impaired blood flow, vessel wall dissection, subintimal hemorrhage, vasoconstriction, and platelet and coagulation factor activation (35). Sigwart et al. (27) were first to report the implantation of stents in 11 patients for abrupt closure complicating angioplasty. Contrary to what was expected, there were no deaths, emergent coronary bypass surgery or myocardial infarction during the hospitalization period, though one patient had late stent occlusion. Larger studies have reported the incidence of subacute stent thrombosis in the setting of threatened or acute vessel closure to range from 2% to 36% with a pooled mean of 10.1% (Table 2). Foley and colleagues (25) found that the incidence of subacute stent thrombosis in 99 patients with elective and 60 patients with emergency stent placement was 1% and 12%, respectively. In fact, most reports (7,22,23,36,37) confirm the several-fold heightened occurrence of stent thrombosis when stents

Table 2. Subacute Stent Thrombosis After Emergency Placement

First Author (ref no.)	Year	No. of Patients	Stent	Thrombosis (no. [%] of patients)	Sequelae of patients with stent thrombosis (no. [%] of patients)*		
					Myocardial Infarction	Revascularization	Death
Sigwart (27)	1988	11	Wall	1 (9.1)	1 (100)	1 (100)	0
de Feyter (28)	1990	15	Wall	1 (6.7)	1 (100)	0	0
Haude (29)	1991	15	P/S	1 (6.7)	0	0	0
Roubin (18)	1992	111	G/R	9 (8.4)	5 (55)	9 (100)	0
Herrmann (21)	1992	55	P/S	9 (16.4)	8 (89)	4 (44)	1 (11)
Fajadet (8)	1992	145	P/S	18 (12.4)	NA	NA	NA
Nath (7)	1993	36	G/R	13 (36.1)	NA	NA	NA
Kimura (9)	1993	23	P/S	3 (13.0)	NA	NA	NA
Hearn (10)	1993	103	G/R	9 (8.1)	4 (44)	3 (33)	1 (11)
Colombo (19)	1993	56	P/S	1 (1.9)	1 (100)	0	0
George (14)	1993	494	G/R	43 (8.7)	20 (47)	29 (67)	2 (5)
Maiello (30)	1993	32	P/S	1 (3.3)	0	1 (100)	0
Lincoff (31)	1993	61	G/R	7 (11.5)	3 (43)	3 (43)	2 (29)
Vrolix (20)	1994	59	Wiktor	10 (16.9)	NA	5 (50)	2 (20)
Sutton (11)	1994	415	G/R	28 (6.7)	21 (75)	NA	NA
Eeckhout (13)	1994	38	Mixed	6 (15.8)	3 (50)	3 (50)	2 (33)
Foley (25)	1994	60	P/S	7 (11.6)	7 (100)	7 (100)	0
Schömig (24)	1994	301	P/S	21 (7.0)	12 (57)	19 (90)	4 (19)
Whitlow (26)	1994	145	Wiktor	14 (9.7)	9 (64)	5 (36)	2 (14)
Metz (32)	1994	101	Mixed	8 (7.9)	NA	NA	NA
Hamm (33)	1994	64	Strecker	12 (18.8)	8 (67)	4 (33)	NA
Pooled	1988–1994	1,928	Mixed	194 (10.1)	103 (61)	93 (61)	16 (12)

*Each patient may have more than one end point reported. NA = data not available; other abbreviations as in Table 1.

are implanted as a "bail-out" compared to elective stent placement, especially if the indication is complete vessel closure.

Clinical presentation. Acute coronary syndromes are commonly associated with intracoronary thrombus (38,39). Intuitively, stent placement in patients with acute myocardial infarction or unstable angina may present a higher risk for stent thrombosis compared to patients with chronic stable angina. Likewise, hemodynamically unstable patients with reduced coronary perfusion pressure may be at increased risk for intrastent thrombus formation. Indeed, in the first clinical report of self-expanding stents (Wallstent), patients with acute coronary syndromes were more likely to develop subacute stent thrombosis (2). Of the 25 patients who developed stent thrombosis, 5 had conditions associated with increased thrombogenicity—unstable angina, myocardial infarction and chronic occlusion. Malosky et al. (40) reported that stent thrombosis occurred in 4.2% of 48 patients with and 1.8% of 57 patients without unstable angina pectoris. Using multiple logistic regression analysis in a statistical model consisting of several clinical and angiographic factors, Nath and colleagues (7) reported the risk of subacute stent thrombosis to be 11 times higher for patients with unstable angina. However, a recent small retrospective analysis (41) suggests that the rate of subacute stent thrombosis is not significantly higher in patients with unstable angina. The reasons for these conflicting reports include different patient cohorts, procedural techniques and indications. The reported incidence of subacute stent thrombosis does vary with different indications for stent placement, even among patients with acute coronary syndromes. For example, Iyer et al. (42) deployed stents emergently in 46 patients within 16 days of myocardial infarction for acute or threatened vessel closure complicating balloon angioplasty, and 5 patients (10.9%) developed subacute stent thrombosis. On the other hand, Marco et al. (43) deployed stents electively in 36 patients with recent (0 to 15 days) myocardial infarction, and only 2 patients (5.6%) developed subacute stent thrombosis. Thus, in general, stent placement in patients with acute coronary syndromes need not be totally avoided, but should be approached cautiously. Risk of subacute stent thrombosis is likely reduced by careful selection of patients.

Lesion-related factors. The coronary anatomy and angiographic characteristics of each lesion are important determinants of subacute stent thrombosis. Some covariates can be assessed objectively, such as vessel size, lesion location and length, but others are limited by angiography, such as the presence of intracoronary thrombus.

Vessel size. A key observation from the early experience of stent implantation was the relationship of stent thrombosis to the size of the target vessel. The likelihood of developing subacute stent thrombosis is inversely proportional to the reference segment diameter—higher rates of thrombosis in smaller vessels (2)—probably as a result of less blood flow and greater amount of metal per luminal area (7,32). Of 210 patients reported by George et al. (14), the occurrence of subacute stent thrombosis for stents ≥3.0 mm, 2.5 mm and 2.0 mm was 7.9%, 8.7% and 25%, respectively. Similarly, Roubin et al. (18) found that 2.5-mm stents, which represented 47% of their stent population, accounted for 77% cases of subacute stent thrombosis. Because of this, most operators will not electively place stents in vessels <3.0 mm (44,45). In fact, in recent randomized trials of balloon angioplasty versus stents, vessels <3.0 mm in diameter by visual estimation were excluded (15,16). On the other hand, the investigators of the STRESS trial (45) reported their experience with stent placement in vessels slightly <3.0 mm (n = 113), measured by quantitative coronary angiography. Interestingly, the restenosis rate was lower in this group of patients with stents compared to conventional balloon angioplasty alone while maintaining an incidence of subacute stent thrombosis lower than in most earlier studies. Overall, vessel size <3.0 mm remains a key predictor of stent thrombosis.

Lesion characteristics and morphology. Angiographic characteristics such as lesion eccentricity (7), degree of stenosis (7,22), ostial involvement (46), presence of intracoronary thrombus and total occlusion may be associated with the occurrence of subacute stent thrombosis. Stent thrombosis is more likely to occur in vessels with poor distal runoff, presence of collateral supply or vessels supplying akinetic or severely hypokinetic myocardium (2). Lesions with greater degree of preprocedural stenosis usually have greater plaque burden or, alternatively, may have occult laminar thrombus. Greater plaque burden may require debulking or greater vessel distension to obtain an optimal result, possibly resulting in more vessel disruption and a more thrombogenic milieu, thereby increasing the risk for stent thrombosis (22). Furthermore, in severely diseased vessels, the atherosclerotic plaque may prolapse through stent struts or articulation sites, increasing the risk for thrombosis.

It has been generally held that one of the most important morphologic characteristics associated with subacute stent thrombosis is the presence of intracoronary thrombus before or after coronary intervention (7). Implanting a foreign body in the presence of thrombus may serve as a nidus for clot propagation. Of 1,054 lesions treated with stents in two large studies, intracoronary thrombus was angiographically evident in 284 (27%) (14,47). The incidence of subacute stent thrombosis among patients with identifiable thrombus was 11%, compared to 7% for those without. Unfortunately, angiography lacks sensitivity in the identification of thrombus, and other means of visualization, such as intravascular ultrasound or angioscopy, may be needed to determine more accurately the relative risk of subacute stent thrombosis from lesion-related thrombus.

Percutaneous recanalization of totally occluded vessels is associated with lower success and increased adverse events with conventional angioplasty. Because the incidence of reclosure is relatively higher following percutaneous revascularization of these lesions, it is not surprising that the risk of subacute stent thrombosis is also increased. Bilodeau et al. (48) reported a subacute thrombotic closure rate of 16% following balloon angioplasty with adjunctive stent placement in totally

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occluded vessels. However, most of the stents were placed in patients with concomitant threatened or abrupt vessel closure. Opposing data from a small study by Almagor and colleagues (49) showed that only 2 (3.1%) of 65 patients had clinically manifest subacute stent thrombosis after elective stent placement in chronic totally occluded vessels. Therefore, stent placement in well selected patients with totally occluded vessels may not increase the risk of symptomatic subacute stent thrombosis excessively. Conversely, stent thrombosis may be underestimated among these patients because reocclusion may occur without symptoms.

Coronary artery dissection during stent deployment is also associated with increased risk for subacute stent thrombosis (22,50) (Fig. 1). In the STRESS study (22), 211 patients received stents electively (per protocol) or as a bail-out procedure (crossover from the balloon angioplasty group). Of the 10 patients who developed subacute stent thrombosis, 40% had coronary dissection evident at final angiography compared to only 9.5% of remaining 201 stent-treated patients.

Site of stent placement. Schömig et al. (24) evaluated the risk of thrombosis following stent placement in different epicardial arteries among 339 patients. The risk of subacute stent thrombosis was lowest in the right coronary artery (2.9%) compared to the left anterior descending artery (10.1%) and the left circumflex artery (7.9%). On a multiple logistic regression model on 243 consecutive stent placements, deployment in the left anterior descending or left circumflex arteries was a determinant for subacute stent thrombosis (51). The lower risk for stent thrombosis in the right coronary artery could be related to more streamline flow characteristics from the lack of major proximal branches and tortuosity. Although the left anterior descending artery has the highest reported risk for subacute stent thrombosis, other investigators found that the excessive risk was attributable to more frequent deployment as a bail-out procedure (52). Therefore, it remains uncertain whether the site of stent placement in the native coronary circulation substantially affects the risk for subacute stent thrombosis.

Saphenous vein grafts. Percutaneous revascularization of saphenous venous grafts is associated with higher risk and less favorable long-term results when compared to percutaneous treatment of native coronary vessels (53). Placement of stents in vein grafts may improve results (Table 3) (26,51,54–62) with a relatively low (2.2%) risk for subacute stent thrombosis. Dorros et al. (61) successfully implanted 159 stents in venous conduits in 95 patients with threatened or acute conduit closure after balloon angioplasty. All stents were at least 3.0 mm in diameter, and the majority were 4.0 mm. Repeat angiography performed 7 days following stent implantation demonstrated only 1 of the 88 conduits to be occluded. More recently, Rechavia et al. (62) reported that none of the 29 patients with stents placed at aortoostial stenosis of vein grafts developed subacute stent thrombosis. The low incidence of subacute stent thrombosis following stent placement in vein grafts may be simply attributable to the large conduit size and the absence of branches. On the other hand, an important factor that needs to be considered before deployment of stents in vein grafts is the adequacy of downstream flow in the recipient vessel, or so-called "runoff." Although the vein grafts may be large and without branches, the distal native circulation may be small and diffusely diseased, thereby reducing blood flow through the stent.

Table 3. Subacute Stent Thrombosis in Saphenous Vein Grafts

First Author (ref no.)	Year	No. of Patients	Stent	Thrombosis (no. [%] of patients)
Urban (54)	1989	13	Wall	0
Leon (55)	1991	192	P/S	2 (1.1)
de Scheerder (56)	1992	69	Wall	7 (10.1)
Strumpf (57)	1992	26	P/S	1 (3.8)
Bernardi (58)	1993	33	P/S	0
Strauss (12)	1994	101	Wall	8 (8.0)
Whitlow (26)	1994	32	Wiktor	0
Eeckhout (51)	1994	28	Mixed	2 (2.1)
Piana (59)	1994	200	P/S	0
Fenton (60)	1994	198	P/S	1 (0.5)
Dorros (61)	1994	95	G/R	1 (1.2)
Rechavia (62)	1995	29	P/S	0
Pooled	1989–1994	1,016	Mixed	22 (2.2)

Abbreviations as in Tables 1 and 2.

Broad classification of lesion morphology may help assess the risk of subacute stent thrombosis following stent placement. Simply stated, the risk for subacute stent thrombosis might be higher in lesions with more complex lesion morphology (22). Applying the most commonly used system, the modified American College of Cardiology/American Heart Association classification (63), Foley et al. (25) found that 40% of patients who developed subacute stent thrombosis had lesions categorized as B2 or C, whereas only 12% of the patients not developing subacute stent thrombosis had the same categories. This study was limited to 60 patients with stents placed as a bail-out procedure. With recent decreasing rates of subacute stent thrombosis, broad classification of lesion morphology has not been reliably associated with risk of developing subacute stent thrombosis in retrospective studies (64). For safety reasons, large randomized trials (15,16) comparing conventional balloon angioplasty to stent placement have thus far excluded patients with recent myocardial infarction or complex lesions.

Stent-related factors. The length and number of stents placed in a lesion as well as the stent geometry were considered to affect the incidence of subacute stent thrombosis. Similarly, stent-specific features such as anticoagulant coatings and stent material may influence the rate of stent thrombosis (Fig. 1).

Length and number of stents. The greater amount of metal present in longer or multiple stents may be more thrombogenic. Limited comparative data are available for stents of differing lengths (4). Roubin et al. (18) reported successful deployment of stents of two different lengths in 115 patients. A short model (12 mm) was placed in 27 patients, and a long (20 mm) model was placed in 88 patients. In this single series,

all nine patients who developed subacute stent thrombosis received the longer stent (4). Multiple stents may be needed in very long lesions or cases of long dissections, thereby heightening thrombotic potential. For this reason, only limited data are again available, because controlled studies have excluded lesions requiring multiple stents. Herrmann et al. (21) placed stents emergently in 56 patients, 11 of whom received multiple stents. The incidence of subacute stent thrombosis for patients receiving single and multiple stents was similarly high (16% vs. 18%). More recently, Colombo et al. (19) used 138 stents in 56 patients to treat acute or threatened closure. Though 57% of the patients received multiple stents, none developed stent thrombosis. Several other investigations (7,14,25) have also concluded that multiple stent deployment was not associated with an increased risk of subacute stent thrombosis. An explanation, in some cases, might be that suboptimal results and persistent dissection are slightly more likely after single stent placement, and this may paradoxically increase the risk for subacute stent thrombosis (19,25). Overall, it is unlikely that the risk for subacute stent thrombosis increases substantially with multiple compared to single stents when they are meticulously deployed without excessive overlapping.

Types of stents. There are several types of commercially available intravascular stent designs and structures that provide different profiles, radial strength, flexibility and perhaps thrombogenicity. Furthermore, the stent strut diameters, which vary from approximately 70 μm (Strecker and Palmaz–Schatz stents) to more than 125 μm (Gianturco–Roubin and Wiktor stents), may also affect thrombogenicity (65). Although no prospective randomized study of different stents is available to make a meaningful direct comparison, the stent thrombosis rate was not different among 81 Palmaz–Schatz (4%), 32 Wiktor (3%), and 21 Gianturco–Roubin (0%) stents in a small retrospective study (66). When data from numerous previous studies were pooled (Tables 1–3), the rate of subacute stent thrombosis appears lowest for Palmaz–Schatz (3.7%), followed by Gianturco-Roubin (7.9%), Wiktor (10.0%), Strecker (12.7%) (67) and Wallstent (13.1%).

Stent material and coating. Most stents are made of stainless steel (Palmaz–Schatz, Gianturco–Roubin and Wallstent) or tantalum (Wiktor and Strecker). Other materials, such as nitinol (an alloy of nickel and titanium) (68), are being tested for lower intrinsic stent thrombogenicity. Another potential method to reduce stent thrombosis is by coating the metallic struts. The coat could selectively alter characteristics by covering the metal surface, neutralizing surface potential, optimizing surface tension and may deliver pharmacologic agents (69). Heparin-bonded, polymer-coated stents were first shown to be effective in reducing thrombosis in rabbit (70) and pig (71) models. The pilot phase of the BENESTENT II trial evaluated the efficacy of this type of stent in 51 patients (72), and none developed stent thrombosis. Local delivery of pharmacologic agents has been tested in different animal models with varying results. The usefulness and cost–benefit of such approaches remain to be evaluated in large-scale randomized trials.

Technique-related factors. Perhaps the greatest contribution in preventing subacute stent thrombosis has been the improvement in stent deployment technique and poststent management. Serruys and DiMario's (73) question, "Who was thrombogenic: the stent or the doctor?" was very appropriate. By defining optimal stent deployment, the requirements for anticoagulation and antiplatelet therapy appear to be quickly evolving (Fig. 1).

Optimization of intra- and postprocedural management. For over a decade, anticoagulation strategies have been studied in animal stent models in order to minimize the risk for stent-related thrombosis. In the first multicenter trial with the Palmaz–Schatz stent (4), patients receiving aspirin but not warfarin experienced a severalfold higher rate of subacute stent thrombosis. In response, anticoagulation regimens were bolstered. Compared to conventional balloon angioplasty, improved angiographic and clinical outcomes following stent deployment were achieved at the cost of a substantial increase in hemorrhagic complications (ranging from 5% to 30%), which substantially increased length of hospitalization and cost (15,16).

With the aid of intravascular ultrasound imaging, it appears that when stents are deployed with struts well apposed to the vessel wall and in full expansion (yielding an optimally large luminal area), the need for anticoagulation is diminished. Following standard balloon inflation pressure of 6–8 atmospheres, Goldberg and colleagues (74) found that only 5 (13%) of 40 patients had adequate stent expansion as assessed by ultrasound despite an acceptable angiographic appearance. Additional balloon inflations with higher pressure and sometimes with a larger balloon diameters were required to obtain satisfactory ultrasound results (74–76). Although some investigators (75,77) have used empirically high balloon inflations pressure of ≥12 atmospheres to achieve an optimal luminal area, others have suggested using a combined intravascular ultrasound and balloon catheter approach, which was developed to enable rapid determination of adequate stent deployment (78).

The evolving paradigm of minimizing stent thrombosis focuses on obtaining optimal stent deployment rather than the intrinsic thrombogenic surface of stents (73). Because platelets have been shown to be the primary component of stent thrombosis (79), with optimal stent deployment, antiplatelet therapy should be sufficient to prevent stent thrombosis during neointimal coverage. The efficacy of using antiplatelet agents alone after stent placement was first demonstrated by Colombo and colleagues (76). Of 359 stent-treated patients, 321 (89%) received only antiplatelet therapy (aspirin ± ticlodipine) after optimal stent deployment with ultrasonic guidance. Only three cases (0.9%) of stent thrombosis occurred. At angiographic follow-up, two additional episodes of stent closure were noted at 3 and 4 months. An ongoing multicenter trial, MUSIC (Multicentre Ultrasound Study In Coronaries), is evaluating the ultrasound criteria proposed by Colombo and colleagues. Cumulatively, 2,630 patients have been reportedly treated with at least 3,141 stents using antiplatelet agents

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Table 4. Subacute Stent Thrombosis Without Oral Anticoagulation

First Author (ref no.)	Year	No. of Patients	Stent	Aspirin	Ticlopidine	IVUS	Thrombosis (no. [%] of patients)
Elias* (80)	1994	79	Wiktor	+	+	–	1 (1.3)
Aubry* (81)	1994	80	Mixed	+	+	–	2 (2.5)
Blengino (82)	1994	74	Mixed	±	±	–	0
Morice* (83)	1994	397	Mixed	+	+	–	6 (1.5)
Carvalho* (84)	1994	87	G/R	+	+	–	1 (1.1)
Jordan* (85)	1994	132	P/S	+	+	–	0
Jordan* (85)	1994	87	G/R	+	+	–	1 (1.1)
Barragan* (86)	1994	238	Mixed	±	+	–	10 (4.2)
Colombo (76)	1995	321	P/S	+	±	+	3 (0.9)
Blasini (87)	1995	60	P/S	+	±	+	0
Colombo (88)	1995	60	G/R	+	±	+	0
Russo (89)	1995	27	P/S	+	+	+	0
Wong (90)	1995	33	NA	+	NA	+	0
Lablanchè (91)	1995	98	Mixed	+	+	–	0
Barragan (92)	1995	208	Mixed	+	+	+	1 (0.5)
Fajadet (93)	1995	119	P/S	+	±	–	1 (0.8)
van Belle (94)	1995	53	Mixed	+	+	–	0
Schühlen (95)	1995	60	NA	+	+	+	0
Colombo (96)	1995	59	Wiktor	+	NA	+	1 (1.5)
Corcos (97)	1995	100	Mixed	+	+	–	1 (1.0)
Tresukosol (98)	1995	33	MS	+	–	–	2 (6.0)
Savalle (99)	1995	60	Mixed	+	–	–	2 (3.2)
Mattos (100)	1995	46	Mixed	+	+	+	0
Lefèvre (101)	1995	150	P/S	+	+	–	1 (0.8)
Pooled	1994–1995	2,630	Mixed	+	±	±	33 (1.3)

*Low-molecular weight heparin was used for 2 to 4 weeks after the procedure. IVUS = intravascular ultrasound; MS = Microstent; + = used; – = not used; ± = used in some patients; other abbreviations as in Tables 1 and 2.

without warfarin, and remarkably, only 33 (1.3%) have developed stent thrombosis (Table 4) (76,80–101). Interestingly, more than two-thirds of these patients did not have intravascular ultrasound imaging.

The preliminary results of these numerous recent trials (Table 4) (80–86,91,93,94,97–99,101) are very encouraging and will likely be confirmed by larger multicenter trials. In addition to studies addressing the importance of ultrasound-guided stent deployment, other methods such as on-line video densitometry with enhancement of radio-opacity of stent struts to define adequate stent deployment are being investigated. Finally, the concomitant need for ticlodipine with aspirin is also being studied in a multicenter trial, MUST (MUlticentre Stent Ticlodipine). Ticlodipine is costly and has several important side effects such as neutropenia, thrombocytopenia and skin rash (102). Therefore, it is suggested that white blood cell and platelet counts be performed every 2 weeks for the first 3 months. Many operators are currently prescribing ticlodipine for only 1 month, the time needed for neointimal coverage of the stent surface. Colombo et al. (76) reported that side effects requiring medication discontinuation was more common in the 252 patients treated with ticlodipine (2.8%) than the 69 patients treated with aspirin alone (0%). Although the rate of stent thrombosis was not significantly different between the aspirin and aspirin with ticlodipine groups, early results from two other clinical trials (Table 4) (97,98) not using intravascular ultrasound suggested a slightly higher rate of stent thrombosis in patients treated with aspirin alone.

Summary

A substantial increase in the understanding of stent thrombosis has taken place over the past several years. The rapidly changing concepts of stent thrombosis can be likened to the early years of balloon angioplasty, when a higher rate of abrupt vessel closure initially occurred. Early stent studies demonstrated a relatively high rate of stent thrombosis that was somewhat improved with aggressive anticoagulation. Subsequent studies have shown an improved outcome with careful patient selection. Although concern for stent thrombosis remains—especially in small vessels, in the setting of abrupt vessel closure, in the presence of intracoronary thrombus or an acute coronary syndrome—contemporary data are encouraging even with reduced anticoagulation. Recent prospective trials have shown, in fact, that by careful case selection, 3% could be an achievable rate of subacute stent thrombosis. Further advances employing high-pressure poststent inflation (16–18 atmospheres) and intravascular ultrasound imaging promise subacute stent thrombosis rates of ≤1%, with antiplatelet therapy alone. Current trials exploring the use of aspirin alone (STRESS III), heparin-coated stents (BENESTENT II) and conjunctive use of platelet glycoprotein IIb/

IIIa inhibitors (EPILOG, Evaluation in PTCA to Improve Long-term Outcome with Glycoprotein IIb/IIIa blockade) may lead to strategies that further reduce the rate of stent thrombosis, perhaps even in the setting of acute myocardial infarction.

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